Therapy for Patients With Chronic Hepatitis B and HIV Co-Infection

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Of the 40 million persons infected with HIV, approximately 10% or 4 million are chronically co-infected with hepatitis B. This high prevalence of co-infection is due to the shared transmission routes of both viruses. The advent of highly active antiretroviral therapy (HAART) has brought the consequences of HIV-HBV co-infection to the forefront since HIV-infected individuals are no longer dying from the opportunistic infections associated with low CD4 counts. Consequences of HIV infection in the setting of HBV include increasing the risk for developing chronic hepatitis B, decreasing the rate of HBeAg seroconversion, increasing the risk for developing cirrhosis and liver-related mortality,[1] and increasing the risk of HAART-related hepatotoxicity. For these reasons, it is important to consider treatment of chronic hepatitis B in the setting of HIV infection.

Since HIV increases the progression of liver disease, it is not known how the treatment guidelines for when to initiate therapy should be altered in the setting of co-infection. In addition to slowing the progression of liver disease, other arguments for starting anti-HBV therapy early include increased ability to tolerate HAART and increased response rates to anti-HBV therapy if CD4 counts are higher. This needs to be balanced by the long-term toxicity of drugs, the increased risk for drug-resistant HBV, and the increased risk for the emergence of drug-resistant HIV since some nucleosides have dual activity against both viruses.

There are limited data on the efficacy of anti-HBV therapy in the setting of HIV infection. To date, the only data on interferon-alfa is with standard interferon-alfa in the era before HAART, so data on pegylated interferon-alfa need to be extrapolated to the HIV population. Since this is an important option when there is no indication for HIV treatment, data are needed on the response to this therapy in the setting of HIV infection.

Of the nucleoside/tide analogues lamivudine, emtricitabine, and tenofovir disoproxil fumarate (TDF) have dual activity against HIV and HBV. The efficacy of lamivudine against HBV is similar to the HIV-negative population, with HBeAg loss occurring in 20% and HBV DNA <400 copies/ml occurring in 40% of treated individuals.[2] However, efficacy is limited by development of lamivudine-resistant HBV, which occurs more rapidly in the HIV-infected population at about 25%/year.[3] Emtricitabine, which is closely related to lamivudine, has similar efficacy to lamivudine, but resistance after 48 weeks was 12%.[4] Tenofovir DF has been studied in over 100 HIV-HBV co-infected persons, but in most studies the results have not been reported in rates of full (HBV DNA <60 IU/ml) or partial virological response.[5] In one retrospective study that included 65 HIV-HBV co-infected patients, 29.6% and 81.6% of HBeAg+ and HBeAg- persons with chronic hepatitis B, respectively, had HBV DNA <60 IU/ml after a median of 12 months of treatment.[6] A randomized controlled trial in 52 HIV-HBV co-infected persons suggested that TDF may be more potent than ADV. After 48 weeks of therapy, HBV DNA decline was approximately one log greater in the 25 persons receiving ADV compared to the 27 persons receiving tenofovir DF.[7] Only 44% of persons receiving 48 weeks of ADV had a partial virologic response ($<10^5$ copies/ml) compared to 100% receiving tenofovir DF.

The two drugs with anti-HBV anti-HIV activity are entecavir and ADV 10 mg. Entecavir (1.0 mg) was given to 51 HIV-HBV co-infected persons with lamivudine-resistant hepatitis B for 24 weeks and compared to 17 persons receiving placebo.[8] The median HBV DNA decline in the entecavir group was 3.66 log copies/ml, with 84% and 6% having a partial and complete virologic response, respectively. Rates of resistance to entecavir in the co-infected population are not known. ADV has only been studied in 31 HIV-HBV co-infected persons followed for 144 weeks.[9] After 144 weeks, 25% had a complete

virologic response, and only two persons became anti-HBe positive. ALT normalization occurred in 14% after 48 weeks and 64% of persons after 144 weeks of therapy. Neither ADV-resistant HBV nor HIV have been detected.

Due to the dual activity and development of resistance of both HIV and HBV to the nucleoside and nucleotide analogues, consideration needs to be given to both viruses when deciding which agents to use for treatment. For individuals who only need their HBV treated, pegylated interferon-alfa, entecavir, and ADV 10 mg are options because they are not active against HIV. If the HIV needs treatment, then it is reasonable to initiate therapy that includes two agents active against HBV in order to delay the development of drug-resistant HBV. One good choice is the combination of tenofovir DF and emtricitabine since they are co-formulated into one pill. This combination is *a propos* even in the situation where lamivudine-resistant HBV exists since the combination may theoretically delay development of tenofovir-resistance. There are limited data on combination therapy for HBV, but data suggest that there may be increased potency and decreased rate of developing resistance.

In summary, little data exist on when treatment for CH-B should be initiated and what the ideal treatment is in the setting of HIV infection. Furthermore, much of the data that exist are not from randomized, clinical trials. Thus, additional data are needed on this subject, especially as HAART is currently being introduced into areas of the world with the highest HIV and HBV endemicity.

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